Job No.: 1505-100760 Ref.: EP0460588B
Translated from German by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

EUROPEAN PATENT APPLICATION
EUROPEAN PATENT OFFICE
EUROPEAN PATENT NO. EP 0 460 588 B1

Int. Cl.[6]:	A 61 K 9/70, A 61 K 9/20
Filing No.:	91109076.9
Filing Date:	June 4, 1991
Publication Date of the Application:	December 11, 1991 Patent Bulletin 91/50
Publication Date of the Announcement of Patent Grant:	August 30, 1995 Patent Bulletin 95/35
Priority:	
Date:	June 7, 1990
Country:	DE
No.:	4018247
Designated Contracting States:	AT BE CH DE DK ES FR GB GR IT LI LU NL SE

A METHOD FOR PRODUCING RAPIDLY DISINTEGRATING PRESENTATION FORMS IN SHEET FORM

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References cited:

EP-A-0 259 749
DE-A-3 744 009
FR-A-2 571 253
GB-A-2 009 597
US-A-4 136 145

The invention concerns presentation forms of drugs, sweets, other foods, cosmetics and the like for oral use or ingestion in sheet form.

Presentation forms of drugs, sweets and other foods as well as cosmetics that are to be used in the oral region or to be ingested by swallowing can be basically either portioned freely by the user or they can already be divided into dosage units by the manufacturer.

Such a preportioned form is particularly common in the field of drugs, in the form of tablets, capsules, coated tablets, pills, ampoules for drinking and the like.

Unlike, for example, forms to be dispensed by the user such as dropping solutions, salves or creams, unintentional misdosage is avoided in this case.

For industrial reasons, a certain minimum size (5 to 6 mm diameter) and a certain minimum weight (about 100 to 200 mg) must be maintained in the case of tablets for these presentation forms to be easily handled. Thus, in the case of highly effective drugs, the amount of auxiliary substances can be around 99% of the weight of the tablet.

Even foods, above all sweets, are often found in individual dispensed forms today (bonbons, sweet tablets, peppermint pastilles, etc.). Here, too, there is a desire, for example, in the case of bonbons, to achieve the desired taste experience with less "auxiliary substance" (usually sugar in this case).

For this reason there have been in recent times a number of proposals for technical solutions aimed at providing presentation forms with smaller amounts of auxiliary substances and at the same time ensuring that these agents can be reliably handled by hand.

One particularly interesting possibility for this is the preparation of active agent carriers in film or sheet form, such as proposed, for example, in DE 35 34 983, DE 27 46 414, BE 637 363, DE 24 32 925 or DE 36 30 603.

According to the currently known preparation methods, such paper-like carriers can first be made without an active agent and then completed by spraying (for example, GB 1 061 557) an active agent-containing solution or by coating or imprinting with a concentrated active agent-containing layer (for example, EP 0 219 762).

For the specialist, however, the common solubilizing or dissolving of active agents and auxiliary agents in water or other solvents (DE 24 49 865) with subsequent spreading or pouring (for example, JP 69026674) and drying will probably be the method of choice. Extrusion under heat has also already been proposed (Research Disclosure, 1986, No. 263, March 145-146 (No. 26341)).

Sheet-like presentation forms offer possibilities for dividing the individual dosages in many different ways.

They can be made in the form of sheets of stamps, in which the portion is not removed from the overall sheet until just before use (for example, BE 637 363, EP 0 219 762). They can also be made in a ribbon-shaped presentation form, i.e., individual doses of various sizes are made by means of perforations (for example, DE 27 46 414). However, especially when an inedible carrier is used (for example, DE 36 30 603), complete separation into individual portions offers itself, since ingestion is in this way hygienic, comfortable and more reliably possible.

Thus, while a number of sheet-like presentation forms and methods of producing them already belong to the prior art, there is still a considerable deficiency in the case of galenical structure, thus in the choice of auxiliary substances and in the concept of the physicochemical fine structure of such sheet carriers.

Here many different objectives must be taken into account: rapid disintegration is desired for many drugs, so that the dosage form can be swallowed rapidly, while for others a temporary adhesion to the oral mucosa is desired, and in other cases, for example, in the case of drugs that are effective only for a short time, a highly delayed disintegration is desired. In the case of sweets, a moderate residence time, for example, of flavors in the mouth is probably to be desired, while a cosmetic sheet-like toothpaste should probably disintegrate as fast as possible and be flexible. Generally, sheet-like presentation forms must not be too fragile, so that the portion can be reliably applied to the intended site. From the manufacturing standpoint, when a carrier is used, both materials must have a precisely adjusted adhesion behavior with respect to each other, on the one hand, to reliably ensure a separation of the dosage unit, for example, by stamping partway through and withdrawing of the die, and on the other hand, to be sure there will be a

good bond to the carrier even during storage. If drying is necessary in production, the goal should be to put the formulation into a spreadable state with as little solvent as possible (preferably water) so that only a little drying energy will have to be employed.

Currently known galenical concepts meet these requirements only fragmentarily. Basic principles of tableting technology are described in DE 27 46 414 in connection with sheet-like ribbons, such as the use of optionally thermoplastic binders and other auxiliary substances, chemical cross-linking or the addition of hydrophobic substances to delay disintegration, the combining of several layers and the use of microencapsulated active agents. Conventional tablet disintegrants were indicated there as disintegration aids for sheet materials. According to our experimental results, these proposals do not meet the requirements of the new drug forms. Classical disintegrants require a porous environment made mechanically stable by interparticulate bonding forces, if they are to cause disintegration by swelling or stored Hooke's deformation energy upon the addition of water.

However, these requirements are not provided in the sheet-like presentation forms, which are always flexible, but only slightly porous. Swelling particles can even delay the disintegration of the sheets due to removal of water.

According to DE 24 32 925, a formulation contains water-soluble cellulose ethers and separating agents, and optionally fillers. However, since a predominate portion of water-soluble polymers regularly require a high addition of water in order to achieve sufficiently low viscosity for spreading or pouring, this structure has high costs for drying in manufacture as a consequence.

In addition, the adhesive bond to the substrate becomes strained because of the strong material shrinkage that occurs in this case. When water-based compounds are spread onto a release [dehesively finished] paper or a release sheet in the production of sheet-like administration forms, the liquid will easily bead up from the substrate or at the minimum form regions with different film thickness because of surface tension. The viscosity can be increased by adding cellulose derivatives, etc., but then spreading through a narrow slot is no longer a simple process. For this reason, according to another source, for example, DE 35 34 981, DE 36 30 603, viscosity forming agents that produce low-viscosity solutions in the heat of the spreader, but immediately thereafter produce gel-like stabilized films upon cooling, which then dry perfectly in air, are preferred, for example, agar-agar or gelatin. However, this method is not satisfactory, since high temperatures cannot be applied in drying because the compound will again bead up. On the other hand, drying of such high-water compounds at low temperatures is uneconomical because of the long residence times in the drying machine.

The same problem arises with a presentation form corresponding to a method described in US-A-4 136 145. This document concerns the preparation of a presentation form with a film

as carrier, in which an active agent is homogeneously dispersed. The application compound contains up to 60 wt% medicament, 0-30 wt% pharmaceutically acceptable filler, a film-forming amount of a water-soluble polymer and solvents or suspension medium, water or organic, volatile, polar solvent. The compound is dried after the film is coated. According to one embodiment it can contain 6-20 wt% film-forming polymer, 48-84[%] solvent or suspension medium and 0.01-2% pharmaceutical active agent.

Another presentation and dosage form for drug-active agents, reagents or the like and a method for producing it is known from EP-A-0 259 749. It has a carrier material in the form of a release paper, a release film or a release sheet, which is provided on one side with an active agent-containing coating, which can be peeled from the carrier material after it is divided into dosage units. The peeled off active agent-containing segments are suitable as oral drugs. For wet application to a release paper, a coating compound of mucilaginous consistency is prepared, then applied to the carrier by means of a roller transfer method, and dried. The formulation of the coating compound is matched to the active agent in it in each case.

Moreover, the preparation of sheet-like administration forms that likewise contain an active component is known from FR-A-2 571 253. The starting point for these forms is a mixture that contains gelatin, gluten, carboxyvinyl polymer, guar gum, lanolin, and it is mixed with a large amount of water, after which one or more active agents is incorporated into the mucilaginous compound, and it is then dried to a residual water content of 10% and applied to a carrier.

For this reason, the invention was based on the problem of making available an individually dosaged sheet-like presentation form that rapidly disintegrates in water and a method for producing it, which requires only a very small added amount of water in order to achieve a sufficiently low viscosity for metering by doctor blade or roller coating, while still yielding a uniformly thick film on a release-coated carrier, as well as adhering well to the carrier in the dry state, while being detachable with sufficient ease from it in later processing, e.g., separation by punching, or before use. This problem is solved in accordance with the invention by a presentation form whose composition was obtained from the substances specified in the main claim in accordance with the production process characterized there.

Other embodiment of the presentation forms are provided in correspondence with the subordinate claims.

The formulations in accordance with the invention can surprisingly be put into a spreadable state with a small addition of a polar solvent.

Unlike formulations according the prior art, they produce uniform films on dehesively finished carriers even in cold state. The products can be separated in a dried state by stamping, so

that the individual dosages remain on a common carrier--the carrier used for spreading and drying.

The presentation form in accordance with the invention disintegrates in the mouth completely within 10 min and can be produced entirely of components that are permissible according to the current food laws of the Federal Republic of Germany. For example, carbonates, phosphate, silicates, sulfates or oxides of alkaline-earth metals, zinc oxide, silicon oxides, cellulose and its derivatives, talc or titanium dioxide can be used as fillers, as well as sparingly soluble sugars or sugar derivatives such as lactose, or starch derivatives like cyclodextrin, provided they are present in the product in essentially undissolved form and thereby satisfy the mechanical properties of a filler.

The term film-forming agent is understood to mean ingredients like sugars, sugar alcohols and their derivatives like cane sugar, sorbitol, mannitol, xylitol, glucose, fructose, lactose, galactose, low-molecular organic acids like succinic acid, malic acid or adipic acid, polyethylene glycol or mixtures of such substances, for example, honey.

A gel-forming agent that can swell in water is necessary as the third important component in accordance with the invention; as a rule it is formed on the basis of polymer carbohydrates, for example, starch and its derivatives, agar-agar, algic acid, arabinogalactan, galactomannan, cellulose and its derivatives, carrageen, dextran, tragacanth and many gums of plant origin. However, synthetic polymers that are soluble or swellable in water can also be used in accordance with the invention: polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid or polyacrylamide, to name only a few. Polypeptides themselves such as gelatin, albumin, collagen or egg white can also be used. Mixtures of gel-forming agents of polymer carbohydrates or their derivatives, gelatin, carboxyvinyl copolymers or polyvinyl alcohol can be advantageously used.

A component that acts as filler, a film-forming agent and a gel-forming agent are necessary components that regularly give the product the desired properties only when they have been processed together according to the properties of the substances in establishing the quantitative formulation. Here a filler can be used, but an active agent that simultaneously acts as filler, can also be used.

The said advantageous properties arise when specific ranges of mixture ratios are maintained:

20-60 wt% film-forming agent, 2-40 wt% gel-forming agent, 0.1 to 35 wt% active agent, up to 40 wt% filler.

The processing can take place by the methods known to the specialist.

As a rule, the starting components are mixed dry and then brought to a spreadable consistency by adding a maximum of 30 wt% of a polar solvent while stirring. The use of homogenizers for intensive mixing or a vacuum to remove air bubbles may be necessary.

Dispersion and grinding devices with freely moveable grinding bodies (ball mills) are preferably used at this point.

Depending on the particular properties of the gel-forming and film-forming agents, it is possible that the use of heat will accelerate the dispersion process and contribute to the desired physicochemical state of the preliminary product. In addition, the addition of water may occasionally be omitted, if the film-forming agent melts.

An extraordinary homogeneous spreadable or extrudable mass results.

The shaping is generally carried out by means of spreading/doctor knife or extrusion methods, in which the compound passes through a gap of specific width, for example, a slot die in extrusion, and thus obtains its external form.

If a solvent is contained in the mixture it is at least partially removed in suitable drying devices, which are known to the specialist.

Advantageously, the product is dried on a carrier, on which it bonds by adhesion even after drying. If for technical reasons it is not possible to achieve sufficient thickness of the preliminary product, two or more layers can be laminated together by using pressure and optionally heat.

Dividing into individual dosages takes place by cutting, stamping and comparable methods that create sheet-like, divided or dividable areas. If dried on a carrier, the presentation form can remain on the carrier after this separation operation until use, which greatly facilitates it ingestion.

The invention is illustrated by means of the following examples:

Example 1:

75 g acetylated starch
62 g honey
55 g calcium sulfate dehydrate
5 g citric acid
50 g water

are mixed in a closed stirrer and heated to 50°C. The mixture is homogenized for 2 h while stirring and then cooled to room temperature. It is stirred for another half hour under vacuum, and water removed by evaporation is replaced.

2 mL peppermint oil is added and homogenously incorporated into the mixture over 5 min by stirring.

The mixture is spread over siliconized paper using a doctor knife with a gap width of 500 μm and dried for 15 min at 80°C.

With an appropriate cutting device, cuts outlining the subsequent shape are made in the dried compound, without damaging the paper carrier.

The material remaining between the individually dosaged presentation forms that now result is removed in process step by mechanical stripping.

To protect against drying out, 12 of these presentation forms are sealed on a common piece of carrier paper in an essentially water vapor impermeable paper/aluminum/ethylene vinyl acetate composite package.

Use: flavor carrier (sweets).

Example 2:

100 g polyethylene glycol (molecular weight about 1500 g/mol)

8 g carboxyvinyl copolymer

are kneaded until homogeneous in a heatable double Z kneader at 80°C (time: 2 h).

70 g lactose

is added and kneaded into the base over 30 min. The temperature is reduced to 50°C. Now

8 g glibenclamide

is added and the batch is kneaded for another 30 min. The hot mixture is filled into a ram extruder preheated to 50°C (useful volume about 150 mL). Immediately it is extruded through a 10 x 1 mm slot die at a rate of about 10 g/min and cooled to solidification on a cold, clean work surface. The strand is cut into 10 mm wide strips with a knife, so that oral drug forms that disintegrate in the mouth, have an active agent content of about 3 mg, and weigh about 80 mg are obtained.

Example 3:

25 g acetylated starch

20 g sorbitol

30 g calcium carbonate

1 g titanium dioxide

22 g water

8 g glycerol

are mixed in a sealed stirring apparatus and heated to 50°C. The mixture is homogenized for another 2 h while stirring and then cooled to room temperature. It is stirred for another half hour under vacuum, and the water removed by evaporation is replaced.

0.5 mL peppermint oil is added and homogeneously incorporated into the mixture over 5 min by stirring. The mixture is spread on siliconized paper with a doctor knife having a gap width of 500 μm, and dried for 10 min at 80°C.

The cuts outlining the subsequent form are made in the dried mixture with a suitable cutting device, without damaging the paper carrier. The material remaining between the individual dosaged presentation forms that are now obtained is removed in a process step by mechanical peeling.

The presentation forms are individually sealed on the carrier paper in an essentially water vapor impermeable paper/aluminum/ethylene vinyl acetate compound packaging.

Usage: instant toothpaste.

Example 4:

600 g acetylated starch

440 g calcium sulfate dehydrate

40 g citric acid

are weighed into a porcelain ball mill loaded with 10 grinding balls (diameter about 4 cm) and mixed dry in the closed mill for 1 h at 10 rpm. A suspension of

20 g titanium dioxide in

550 g water

is added, and the mixture is agitated under the same conditions for another hour.

500 g honey is added; the mixture is homogenized for another 2 h at 10 rpm. Finally, 16 mL peppermint oil is added and the agitation is continued for 18 h.

Further processing of the resulting mixture is carried out as indicated under Example 1.

Claims

1. Process for the production of a sheet-like, individually dosed administration form of drugs, confectionary, other foodstuffs cosmetics and the like for oral application or intake, which administration form rapidly disintegrates in water, whereby said administration form contains a base mass on a carrier or consists of the base mass without a carrier, characterized by the following steps:

   a) 20 to 60%-wt. of film forming agent(s), 2 to 40%-wt of gel-forming agent(s), 0.1 to 35%-wt. of active substance and a maximum of 40%-wt. of an inert filling agent are

intimately premixed in dry condition
b) the initial mixture thus obtained, comprising film former, gel former, active substance and filling agent, is given a spreadable consistency by adding up to 30%-wt. of a polar solvent, relative to the above-mentioned components, while stirring, whereby, in order to accelerate the dispersion process and to produce the desired physicochemical properties of the initial product, from case to case both heat and homogenizers and/or vacuum are employed;
c) the mass of the initial product is applied to a release paper or a release film, the thickness of the mass amounting to 0.003 to 4 mm, preferably 20 to 400 µm, and particularly preferred 70 to 150 µm.
d) the polar solvent is, after application of the layer, at least partially removed by the action of heat and/or low pressure.

2. The process according to claim 1, characterized in that the spreadable mass is manufactured without the addition of a solvent but employing a film former melting at the process temperature.

3. The process according to claim 1, characterized in that the mixing of the components according to a) is carried out under partial vacuum.

4. The process according to claim 1, characterized in that the mixing of the components according to a) is carried out in a ball mill.

5. The process according to claim 1, characterized in that as film formers there are used, substantially, mixtures of monomeric or oligomeric sugars or sugar derivatives of sugar alcohols or polyethylene glycol.

6. The process according to claim 1, characterized in that as gel formers there are used polymeric carbohydrates or the derivatives thereof, gelatin, carboxyvinyl copolymers, polyvinyl alcohol, or mixtures of said substances.

7. The process according to claim 1, characterized in that as active substance a pharmacologically active substance is used.

8. The process according to claim 1, characterized in that as filler calcium carbonate, calcium sulfate, a calcium phosphate, a carbohydrate present in a crystalline or partially crystalline form, talc, titanium dioxide, zinc oxide, magnesium stearate, or a mixture of those sub-

stances is used.

9. The process according to claim 1, characterized in that the administration form comprises at least two active substance-containing layers.

10. The process according to claim 1, characterized in that the administration form is present in portions which are individually dosed